MITOS.002A PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Kameron W. Maxwell et al.
Appl. No.	:	10/675,225
Filed	:	September 29, 2003
For	:	NITROXIDE RADIOPROTECTOR FORMULATIONS AND METHODS OF USE
Examiner	:	James William Rogers
Group Art Unit	:	1618

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANT'S REPLY BRIEF

Mail Stop Appeal Brief -- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Reply Brief relates to an appeal to the Board of Patent Appeals and Interferences of the final rejection set forth in a Final Office Action mailed September 15, 2006 in the above-captioned application. In an Examiner's Answer dated March 6, 2008, the Examiner maintained all of the grounds of rejection in the Final Office Action, supported by new argument. Pursuant to 37 C.F.R. § 41.41 and M.P.E.P. § 1208, Appellant provides in the following Reply Brief a detailed explanation of why the grounds of rejection, as argued in the Examiner's answer, are improper.

I. Status of the Claims

The above-identified application was filed with 25 claims. Claims 1-25 were rejected by the Examiner in an Office Action mailed April 11, 2006. Subsequently, Claims 11, 13, 16, 24, and 25 were amended and Claim 18 was canceled. Claims 1-17 and 19-25 were finally rejected in an Office Action mailed September 15, 2006. Subsequent to that Office Action, Claim 24 was amended. The amendment to Claim 24 was not entered for purposes of appeal by the Examiner in an Advisory Action mailed February 16, 2007, in which the Examiner indicated that Claims 1-17 and 19-25 remained rejected. Accordingly, Claims 1-17 and 19-25 remain under appeal. A listing of the claims is attached hereto in the Claims Appendix, which remains unchanged from those in the Appellant's original brief.

I. Arguments Raised by Examiner's Answer

A. Mitchell (U.S. Patent No. 5,462,946) disclose a gel

The Examiner acknowledged that Mitchell does not expressly state the compositions are gels. Examiner's Answer, pp. 9-10. However, the Examiner has argued that the definition of a gel was broad enough to encompass a cream or lotion, and that the claimed invention in its present state is not limiting enough to exclude lotions or creams. Examiner's Answer, pp. 6-7. Thus, the Examiner argues that Mitchell discloses gels. As a result, the Examiner has argued that the claims are anticipated. Examiner's Answer, pp. 6-8.

B. Mitchell allegedly inherently discloses a low-residue gel

The Examiner has argued that the ingredients disclosed by Mitchell inherently have the same properties as a low-residue gel. Examiner's Answer, pp. 6-7. In addition, the Examiner has argued that the term "'low-residue' is a relative term, and as such it is unclear how limiting the recitation is in regards to the amount of residue that can be present for a composition to still read on appellant's claimed invention." Examiner's Answer, pp. 3, 4 and 7. As a result, the Examiner has argued that the claims are anticipated. Examiner's Answer, pp. 6-8.

C. Mitchell allegedly inherently discloses a low-residue thickened liquid

The Examiner has argued that the ingredients disclosed by Mitchell inherently have the same properties as a low-residue thickened liquid. Examiner's Answer, pp. 5-7. As noted above, the Examiner has argued that the term "'low-residue' is a relative term, and as such it is unclear how limiting the recitation is in regards to the amount of residue that can be present for a composition to still read on appellant's claimed invention." Examiner's Answer, p. 7. As a result, the Examiner has argued that the claims are anticipated. Examiner's Answer, pp. 6-8.

D. The combination of Golz-Berner (U.S. Patent No. 5,462,946) and Mitchell allegedly renders the claimed low-residue compositions obvious

The Examiner has stated that "Golz-Berner was used primarily in combination with Mitchell for its disclosure of cosmetic active substances to protect the skin and the use of solvents, carriers and hydrogels, which Mitchell did not disclose." Examiner's Answer, p. 9. The Examiner has argued that "the fact that Golz-Berner discloses glycerine in the examples does not mean that Golz-Berner teaches away from applicants claimed invention." Examiner's Answer, p. 9. As a result, the Examiner has argued that the claims are obvious. Examiner's Answer, pp. 8-11.

II. Reply to Arguments

A. Mitchell does not disclose a gel

Applicants respectfully submit that the gel recited in the rejected claims is not disclosed by Mitchell. It is incorrect to equate gels (generally understood in common usage to be stiff materials with at least some structural integrity, e.g., semisolid or gelatinous) with Mitchell's various types of viscous liquids (which would be expected to flow like liquids, albeit more slowly as they become more viscous).

The Examiner has pointed to Applicants' specification, paragraphs [0091]-[0097], as teaching that a gel essentially has the same scope of the ointments, creams and lotions disclosed by Mitchell. This is incorrect. As the Examiner has noted, Applicants' disclosure at paragraphs [0091]-[0097] teaches that "a gel relates to a semisolid system of either suspensions made up of

small inorganic particles or large organic molecules interpenetrated by a liquid. Generally, if left undisturbed for some time, gels may be in a semisolid or gelatinous state." Applicants' description is consistent with the definition of a "gel" according to the U.S. Food and Drug Administration's Center for Drug Evaluation and Research Data Standards Manual[1] (hereinafter referred to as the "Manual"). For at least the reasons presented below, a gel is ***not*** the same as an ointment, cream, lotion, aerosol or any other dosage form disclosed by Mitchell.

According to the Manual, a "gel" is "a semisolid dosage form that contains a ***gelling agent to provide stiffness*** to a solution or a colloidal dispersion." (Emphasis added.) In contrast, the Manual defines an "ointment" as "[a] semisolid dosage form, usually containing < 20% water and volatiles and > 50% hydrocarbons, waxes, or polyols as the vehicle." A "cream" is defined by the Manual as "an emulsion, semisolid dosage form, usually containing > 20% water and volatiles and/or < 50% hydrocarbons, waxes, or polyols as the vehicle." "Lotions" are defined simply as "[a]n emulsion, liquid dosage form." An "aerosol"[2] is defined by the Manual as "a product that is packaged under pressure and contains therapeutically active ingredients that are released upon activation of an appropriate valve system." A "spray" is defined by the Manual as "a liquid minutely divided as by a jet of air or steam." "Drops" is defined by the Manual as "a solution which is usually administered in a drop-wise fashion." A "solution" is defined by the Manual as "a clear, homogeneous liquid dosage form that contains one or more chemical substances dissolved in a solvent or mixture of mutually miscible solvents." Thus, it is clear from standard definitions that none of the dosage forms disclosed by Mitchell cited by the Examiner are defined as containing a gelling agent to provide stiffness as required by the Manual's definition of a gel. Furthermore, at no point do Mitchell discloses addition of a gelling agent to any dosage form in order to provide stiffness to the dosage form. Therefore, Mitchell does ***not*** disclose a gel. As a result, the art of record fails to disclose each and every element set forth in the rejected claims.

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[1] Available at http://www.fda.gov/cder/dsm/DRG/drg00201.htm.

[2] Moreover, the aerosols, drops, and sprays of Mitchell are not topical formulations designed to protect the skin, but are rather for inhalation, placement in the eyes, or application to plants. Mitchell '946 at col. 2, line 63 – col. 3, line 30.

Accordingly, Appellants respectfully submit that the claims are not anticipated by the art of record.

B. Mitchell does not inherently disclose a low-residue gel

Applicants respectfully submit that Mitchell does not inherently disclose a low-residue gel.

With regard to establishing inherency of a certain result, the M.P.E.P. sets forth the following:

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The ***mere fact that a certain thing may result from a given set of circumstances is not sufficient.***'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

M.P.E.P. § 2112(IV), emphasis added.

As discussed above, it is clear from standard definitions that none of the dosage forms disclosed by Mitchell are defined as containing a gelling agent to provide stiffness as required by the Manual's definition of a gel. As clearly set forth in M.P.E.P. § 2112(IV), the mere fact that a certain thing (*e.g.*, a gel) ***may*** result from a given set of circumstances (*e.g.*, addition of a gelling agent to an ointment, cream, lotion, or aerosol, drop or spray) is ***not*** sufficient to establish inherency of the gel. Furthermore, Mitchell does not disclose that a gelling agent to provide stiffness is present in, or may be added to, any of the disclosed dosage forms. Therefore, Mitchell does ***not*** inherently disclose a gel.

As discussed in Applicants' specification, the use of an ointment, cream or lotion form of a radioprotective composition shortly before the administration of radiation leaves a residue or film that leads to potentially severe topical burning. *See* specification at pp. 2, 15. This is clear from standard definitions of these terms. As discussed above, the Manual defines an "ointment" as "[a] semisolid dosage form, usually containing < 20% water and volatiles and > 50%

hydrocarbons, waxes, or polyols as the vehicle." Dosage forms containing such significant amounts of residue-producing substances will ***not*** be "low-residue." Thus, based on the definitions of "ointment" widely recognized in the art, it would seem that a "low-residue gel" is not even a possible result from any circumstances relating to an ointment. As discussed above, a "cream" is "an emulsion, semisolid dosage form, usually containing > 20% water and volatiles and/or < 50% hydrocarbons, waxes, or polyols as the vehicle." In addition, based on standard definitions (provided above), "lotions," "aerosols," "drop," and "sprays" are not limited to low-residue forms. Indeed, guidelines to patients undergoing radiation therapy generally counsel specifically against the use of lotions on the treated area during therapy. As clearly set forth in M.P.E.P. § 2112(IV), the mere fact that a certain thing (*e.g.*, a low-residue gel) ***may result*** from a given set of circumstances (*e.g.*, addition of a very minor amount of gelling agent to the cream, lotion, aerosol, spray or drops, and ensuring that the resulting dosage form has low enough amounts of residue-producing substances such that it will be low-residue) is ***not sufficient*** to establish inherency of the low-residue gel. As such, Mitchell does ***not*** inherently disclose a low-residue gel. As a result, the art of record fails to disclose each and every element set forth in the rejected claims.

Applicants would like to address the Examiner's assertion that "'low-residue' is a relative term and as such it is unclear how limiting the recitation is in regards to the amount of residue that can be present for a composition to still read on appellant's claimed invention." Examiner's Answer, pp. 8-11. This is incorrect. While Applicants note that the claims have not been rejected under 35 U.S.C. § 112, second paragraph, Applicants respectfully point out to the Examiner that Applicants' specification makes abundantly clear that the "low-residue" is defined in terms of residue-induced burning in the specification: "[a]s used herein, 'low-residue' refers to formulations that can be applied to a patient, shortly before undergoing radiotherapy, without leaving a residue capable of enhancing a bolus effect upon delivering radiotherapy to the treated area." Specification at ¶ [0084]. Applicants' specification teaches that low-residue formulations can be achieved by including only a very minor amount of a gelling agent, which remains behind after evaporation of the solvent together with the active ingredient. *See* specification at ¶ [0064]. Furthermore, the present specification makes clear that prior art creams, lotions, shampoos, cream rinses, and ointments such as those disclosed in Mitchell leave residues on the skin that can result in severe burning when applied shortly before the administration of radiotherapy. *See*

specification at ¶ [0073]. In light of the explicit definition of the term in the specification, Applicants submit that the term "low-residue" is clear.

Accordingly, Appellants respectfully submit that the claims are not anticipated by the art of record.

C. Mitchell does not inherently disclose a low-residue thickened liquid

Applicants respectfully submit that Mitchell does not inherently disclose a low-residue thickened liquid.

The M.P.E.P. sets forth that inherency is not proper when based on what would result due to optimization of conditions, not what was necessarily present in the prior art:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (***reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art***).

M.P.E.P. § 2112(IV), emphasis added.

As discussed in detail above, dosage forms such as ointments, creams, lotions, aerosols, sprays or drops are not *necessarily* low-residue formulations. Even if it there is a possibility that one of these dosage forms could be formulated such that it was low-residue, this is not enough to establish inherency of the low-residue nature of the dosage form. Inherency may not be established by probabilities or possibilities. M.P.E.P. § 2112(IV).

The avoidance of the problem of residue-induced burning by the described and claimed low-residue formulations was first recognized by Applicants. *See* specification at ¶ [0064]. Indeed, "low-residue" is explicitly and unambiguously defined in terms of such burning in the specification: "[a]s used herein, 'low-residue' refers to formulations that can be applied to a patient, shortly before undergoing radiotherapy, without leaving a residue capable of enhancing a bolus effect upon delivering radiotherapy to the treated area." Specification at ¶ [0084].

The Examiner has argued that it is deemed inherent, and a "normal part of experimentation by someone skilled in the art" to adjust the formulation to achieve the properties of the formulations recited in the rejected claims. Examiner's Answer, pp. 3-4. However, as noted above, it is not proper to base inherency on speculating what would result due to optimization of conditions, instead of focusing on was *necessarily present* in the prior art. Mitchell does not inherently disclose a low-residue thickened liquid with an amount of residue insufficient to enhance burning to the skin or mucous membranes when radiotherapy is applied. As a result, the art of record fails to disclose each and every element set forth in the rejected claims.

Accordingly, Appellants respectfully submit that the claims are not anticipated by the art of record.

D. The combination of Golz-Berner with Mitchell renders the prior art unsatisfactory for its intended purpose

Applicants respectfully submit that the proposed combination of Golz-Berner and Mitchell renders the Golz-Berner reference unsatisfactory for its intended purpose.

The Examiner acknowledges that Golz-Berner discloses "a cosmetic preparation of active substances to protect the skin (including Tempol) in the form of a gel composed of hydrogels (including natural polymers such as hydroxymethylcellulose), solvent (including ethanol) and ***other ingredients***." Examiner's Answer, p. 4, emphasis added. However, the Examiner has stated that it is not relevant that Golz-Berner discloses Tempol in a cream including phospholipids and glycerine. Examiner's Answer, p. 8. This is incorrect.

In combining references to make an obviousness rejection, the proposed modification ***cannot*** render the prior art unsatisfactory for its intended purpose. M.P.E.P. §2143.01(V). In addition, like all references cited in an obviousness rejection, Golz-Berner must be considered in its ***entirety***, including portions that would lead away from the claimed invention. *See W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51 (Fed. Cir. 1983); M.P.E.P. §2141.02(VI).

As discussed below, the proposed combination of Golz-Berner and Mitchell renders the Golz-Berner reference unsatisfactory for its intended purpose. Furthermore, when Golz-Berner

is considered in its entirety, its disclosure would ***not*** lead one of skill in the art to a low-residue gel or low-residue thickened liquid.

Golz-Berner is concerned with the preparation of cosmetic preparations, with one stated objective of the invention being "to provide a preparation of active substances that keeps its radical protection potential over a long period of time." Golz-Berner at col. 1, lines 52-54, emphasis added. In contrast, Applicants' specification makes clear that the low-residue formulations can be achieved by including only a very minor amount of a gelling agent, which remains behind with the active ingredient after evaporation of the solvent. *See* specification at ¶ [0064]. Thus "98%, 99% or more of the carrier for the drug can disappear prior to radiotherapy, greatly reducing or eliminating burning due to the bolus effect." *Id.*

The Examiner's proposed combination of Golz-Berner and Mitchell is not proper, because the Examiner has isolated out of Golz-Berner only the disclosure of a hydrogel and Tempol, ignoring all of the other ingredients in that cosmetic composition. The express purpose of Golz-Berner's cosmetic preparation is "to provide a preparation of active substances that keeps its radical protection potential over a long period of time." Thus, removing all but two of the ingredients would render the composition unsatisfactory for its intended purpose, because it would no longer provide a preparation of active substances that keeps its radical protection potential over a long period of time. Therefore, the combination of Golz-Berner and Mitchell is not proper.

Furthermore, Applicants note that Golz-Berner does not teach or disclose low-residue dosage forms. As noted above, the dosage form disclosed by Golz-Berner contains phospholipids and glycerine; Golz-Berner does not teach a dosage form for Tempol containing only a very minor amount of gelling agent. Thus, the deficiencies of Mitchell are not remedied by the disclosure of Golz-Berner. As a result, even if properly combined, the art of record fails to teach or suggest all limitations of the claims.

Accordingly, Appellants submit that the claims are not obvious over the art of record.

III. Claims Appendix

Attached hereto is a "Claims Appendix" containing a copy of the finally rejected claims in the present case.

III. Conclusion

In view of the foregoing arguments, Appellants respectfully submit that the rejections of the pending claims are improper and should be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 6, 2008

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IV. CLAIMS APPENDIX

1. (Original) A pharmaceutical composition for use in ameliorating an effect of radiotherapy on skin, mucous membranes, or hair follicles comprising:

a solvent; and

an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel.

2. (Original) The pharmaceutical composition of Claim 1, wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

3. (Original) The pharmaceutical composition of Claim 1, wherein the solvent is selected from the group consisting of water, urea, alcohols, and glycols.

4. (Original) The pharmaceutical composition of Claim 3, wherein the solvent is an alcohol selected from the group consisting of methanol, ethanol, propanol, and butanol.

5. (Original) The pharmaceutical composition of Claim 3, wherein the glycol is selected from the group consisting of ethylene glycol and propylene glycol.

6. (Original) The pharmaceutical composition of Claim 1, wherein the effect of radiotherapy is selected from the group consisting of skin conditions, mucous membrane conditions, hair follicle conditions, cytotoxicity, and polynucleic acid damage.

7. (Original) The pharmaceutical composition of Claim 6, wherein the skin condition is selected from erythema, folliculitis, fibrosis, dry desquamation, moist desquamation, hyperpigmentation, and dermatitis.

8. (Original) The pharmaceutical composition of Claim 6, wherein the mucous membrane condition is selected from oral mucositis and proctitis.

9. (Original) The pharmaceutical composition of Claim 6, wherein the hair follicle condition is alopecia.

10. (Original) The pharmaceutical composition of Claim 1, wherein the effective prophylactic or therapeutic amount of a nitroxide radioprotector is an amount from about 0.01 to about 100 mg/ml of the total composition.

11. (Previously presented) The pharmaceutical composition of Claim 1, further comprising a polymer selected from the group consisting of ethylene polymers, acrylic polymers, polyvinylpyrrolidones (PVPs), polyvinyl copolymers, cellulose polymers, natural polymers, polystyrene polymers, silicone polymers, and inorganic polymers.

12. (Original) The pharmaceutical composition of Claim 1, having a viscosity such that the nitroxide radioprotector will remain in contact with a treated area for a sufficient period of time to allow absorption of a pharmacologically effective amount into said treated area.

13. (Previously presented) A pharmaceutical composition for use in ameliorating an effect of radiotherapy to skin or mucous membranes, comprising:

a solvent; and

an effective prophylactic or therapeutic amount of a nitroxide radioprotector in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel or low-residue thickened liquid that does not leave an amount of residue sufficient to enhance burning to the skin or mucous membranes when radiotherapy is applied.

14. (Original) The pharmaceutical composition of Claim 13, wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

15. (Original) A pharmaceutical composition for use in preventing or treating alopecia comprising:

a solvent; and

an effective prophylactic or therapeutic amount of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl in solution in the solvent, wherein the pharmaceutical composition is in the form of a low-residue gel.

16. (Previously presented) A method of treating a patient, comprising topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat harmful side effects caused by radiotherapy, wherein the nitroxide radioprotector is in solution in a solvent, and the solution is in the form of a low-residue gel or a low-residue thickened liquid.

17. (Original) The method of Claim 16 wherein the nitroxide radioprotector is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

18. (Canceled)

19. (Original) The method of Claim 16, wherein the solvent is selected from the group consisting of water, urea, alcohols, and glycols.

20. (Original) The method of Claim 16 where the harmful side effect is selected from the group consisting of skin conditions, mucous membrane conditions, hair follicle conditions, cytotoxicity and polynucleic acid damage.

21. (Original) The method of Claim 20 wherein, the skin condition is selected from erythema, folliculitis, fibrosis, dry desquamation, moist desquamation, hyperpigmentation, and dermatitis.

22. (Original) The method of Claim 20 wherein, the mucous membrane condition is selected from oral mucositis and proctitis.

23. (Original) The method of Claim 20, wherein the hair follicle condition is alopecia.

24. (Previously presented) A method of treating a patient, comprising:

topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent;

evaporating solvent; and

applying radiotherapy to said patient.

25. (Previously presented) A method of treating a patient, comprising:

topically applying a sufficient amount of a nitroxide radioprotector to prevent or treat a harmful side effect caused by radiotherapy, wherein the nitroxide radioprotector is in solution in solvent, has a sufficient viscosity such that it is retained in place on the patient, and the solution is in the form of a low-residue gel or a low-residue thickened liquid; and

applying radiotherapy to said patient.